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Autoimmune Pancreatitis: Etiology, Pathogenesis, Clinical Findings and Treatment. The Japanese Experience

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Summary

A concept of "autoimmune pancreatitis" has recently been proposed. Computed tomography, magnetic resonance imaging or ultrasonography can demonstrate the diffusely enlarged pancreas with its so called "sausage-like" appearance. Hypergammaglobulinemia, increased serum levels of total IgG or IgG4, positive autoantibodies such as antinuclear antibody, anti-lactoferrin antibody, anti-CA-II antibody and rheumatoid factor have often been observed in patients with autoimmune pancreatitis. Microscopic findings have shown fibrotic changes involving infiltration of lymphocytes and plasmacytes, and often obliterative phlebitis in the pancreas. The major lymphocytes infiltrating the zone around the pancreatic duct were T cells producing IFN-g. HLA-DR was also expressed on the pancreatic duct and acinar cells as were lymphocytes. It is important to make the diagnosis of a diffusely enlarged pancreas based on clinical laboratory findings and pancreatic imaging such as narrowing pancreatogram. Laboratory data, pancreatic images and diabetes mellitus in most patients improved after steroid treatment.
In conclusion, autoimmune pancreatitis appears to be a unique clinical entity.

Introduction

Idiopathic pancreatitis, in which obvious causes are not detected, accounts for about 30-40% of cases of chronic pancreatitis [1]. Since Sarles *et al*. observed the first case of pancreatitis with hypergammaglobulinemia [2], the occasional coexistence of pancreatitis with other autoimmune diseases such as Sjögren's syndrome (SjS) [3], primary sclerosing cholangitis (PSC) [4, 5] or primary biliary cirrhosis (PBC) [4] has been reported. These findings support the hypothesis that an autoimmune mechanism may be involved in the pathogenesis and pathophysiology in some patients with pancreatitis [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17], which leads us to the concept of autoimmune-related pancreatitis [15], which is called "autoimmune pancreatitis" (AIP) [8]. Recently, the concept of AIP is thought to be acceptable as a new clinical entity due to its unique clinical and histological findings. Several hundred cases of AIP have been reported in the Japanese literature [5, 8, 9, 10, 11, 12, 13, 18, 19, 20]. We encountered 30 cases of AIP in a total of 620 cases of chronic pancreatitis (5%). Males are predominant and most patients were diagnosed at middle or advanced age (mean: 58 years). In this paper, we report recent etiopathological and clinical findings based on our experience.

Table 1. Clinical characteristics of autoimmune pancreatitis.

Increased levels of serum gammaglobulin or IgG
Presence of autoantibodies
Diffuse enlargement of the pancreas
Diffusely irregular narrowing of the main pancreatic duct on ERCP images
Fibrotic changes with lymphocyte infiltration
No symptoms or only mild symptoms without acute attacks of pancreatitis
Rare pancreatic calcification
Rare pancreatic cysts
Occasional association with other pathologies such as
Diabetes, sclerosing cholangitis similar to PSC, sialoadenitis,
Interstitial nephritis and retroperitoneal fibrosis
Effective steroid therapy.

Definition and Concept of AIP

Although the pathogenesis and patho-physiology of AIP are still unclear, clinical aspects have been accumulated [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. The characteristic findings in the most cases of AIP [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16] can be summarized as follows: i) increased levels of serum gammaglobulin or IgG; ii) the presence of autoantibodies; iii) diffuse enlargement of the pancreas; iv) diffusely irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangio-pancreatography (ERCP) images; v) fibrotic changes with lymphocyte infiltration; vi) no symptoms or only mild symptoms, usually without acute attacks of pancreatitis; vii) rare pancreatic calcification; viii) rare pancreatic cysts; ix) occasional association with other lesions such as diabetes, sclerosing cholangitis similar to primary sclerosing cholangitis (PSC), sialoadenitis, interstitial nephritis and retroperitoneal fibrosis, and x) effective steroid therapy (Table 1). Recently, “Diagnostic Criteria for Autoimmune Pancreatitis 2002” containing three criteria, pancreatic imaging, laboratory data, and histopathological findings has been proposed by the Japan Pancreas Society (Table 2) [3]. The occasional coexistence of pancreatitis with other systemic exocrinopathies, bile ductal lesions, and diabetes mellitus (DM) have led to the concept of "a complex syndrome" [4], "dry gland syndrome" [5] and "autoimmune exocrinopathy”. Other names such as "chronic inflammatory sclerosis of the pancreas", "lymphoplasmacytic sclerosing pancreatitis" (LPSP), "pancreatitis showing the narrowing appearance of the pancreatic duct" (PNPD), "pseudotumor of the pancreas", "tumefactive chronic pancreatitis", and "IgG4 related autoimmune disease" have been proposed for cases similar to AIP [18, 19]. Recently, histological findings such as LPSP are thought to be extremely similar to AIP [18].

Table 3. Autoimmune pancreatitis and associated diseases (n=30, M/F 18/12, mean age 58 years).

No complications	1 (40%)
Diabetes mellitus	15 (50%) (1 type Ia, 14 type II)
Sclerosing cholangitis	8 (27%)
Rheumatoid arthritis	6 (23%)
Sjögren's syndrome	5 (17%)
Nephropathy	3 (12%)
Retroperitoneal fibrosis	3 (10%)

Associated Lesions (Table 3)

Patients with AIP often show bile duct lesions such as intra-pancreatic stenosis or a sclerotic appearance of the extra-pancreatic bile duct

Table 2. Diagnostic criteria 2002 of autoimmune pancreatitis proposed by the Japan Pancreas Society.

1. Pancreatic imaging studies show diffuse narrowing of the main pancreatic duct with irregular walls and diffuse enlargement of the pancreas.
2. Laboratory data demonstrate abnormally elevated levels of serum gamma-globulin, and/or IgG, or the presence of autoantibodies.
3. Histopathological examination of the pancreas shows fibrotic changes with lymphocyte and plasma cell infiltration.

For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3.

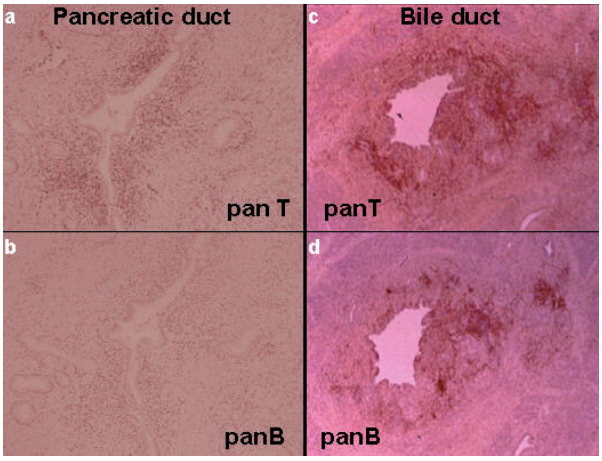

Figure 1. Immunohistochemistry of the pancreas in autoimmune pancreatitis. Immunohistochemistry showed T-cells mainly infiltrated around the pancreatic duct (x 250). **a.** pan T cells (pancreatic duct); **b.** pan B cell (pancreatic duct); **c.** pan T cell (intra-pancreatic bile duct); **d.** pan B cell (intra-pancreatic bile duct).

similar to PSC. Unlike PSC, biliary lesions in AIP usually improve by administering steroids, which suggests that the mechanism of the development of biliary lesions in AIP may be different from typical PSC. DM is often (43-68%) observed in AIP and the majority of patients have type II DM; some improve after steroid therapy. Although the mechanism is obscure, cytokines from T cells and macrophages suppressing the function of islet beta-cells may be down-regulated by steroids. Eleven of our 30 cases did not have any other lesions, while 19 patients with AIP had one or more associated lesions. Fifteen patients (50%) had diabetes, 8 sclerosing cholangitis (27%), 6 rheumatoid arthritis (23%), 5 sialoadenitis (17%), 3 renal dysfunction (10%), and 3 retroperitoneal fibrosis (10%). It has been noted that there is a possibility of development of other complications even in the patients diagnosed as having only pancreatitis [10].

Histopathology

Microscopic findings in AIP are consistent with lymphoplasmacytic sclerosing pancreatitis as previously reported by Kawaguchi *et al.* [6]: i) diffuse lymphoplasmacytic infiltration with pronounced acinar atrophy; ii) marked fibrosis of the contiguous soft tissue as well as the total pancreas similar to retro-peritoneal fibrosis; iii) obliterated phlebitis in and around the pancreas involving the portal vein; iv) inflammatory wall thickness of the common bile duct (CBD) and gallbladder; and v) the minor salivary gland in the lip biopsy having inflammation similar to the pancreatic lesion or Sjögren's syndrome. In addition to these findings, in AIP, T-cells, which are usually HLA-DR+ CD4+ or HLA-DR+ CD8+ cells, predominantly infiltrate around the pancreatic duct over B cells (Figure 1) [10]. Although the mechanism is still unclear, the histological differences between lymphoplasmacyte and T cell dominance may suggest the different stages of the diseases.

Clinical Symptoms

Patients with AIP usually have no or only slight discomfort in the epigastrium or back, and symptoms related to other associated diseases [2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. The clinical symptoms are different from those in the cases of acute or severe pancreatitis. In our 30 patients, 19 patients had jaundice (63%), 8 had abdominal pain (27%), and 6 had back pain (20%). Obstructive jaundice due to the stenosis of the CBD or sclerosing cholangitis is characteristic in AIP as compared to other types of pancreatitis. Steroid therapy is usually effective for stenosis of the bile duct associated with AIP and improves clinical and laboratory findings [9, 10, 11, 12, 13].

Pancreatic and Biliary Imaging

Computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (US) show the diffusely enlarged pancreas with its so called "sausage-like" appearance (Figure 2), and a capsule-like rim which appears to have low density on CT and to be hypo-intense on T2-weighted MR images, and shows delayed enhancement on dynamic MR imaging [20, 21]. Pancreatic calcification or pseudocyst is seldom observed. F-18

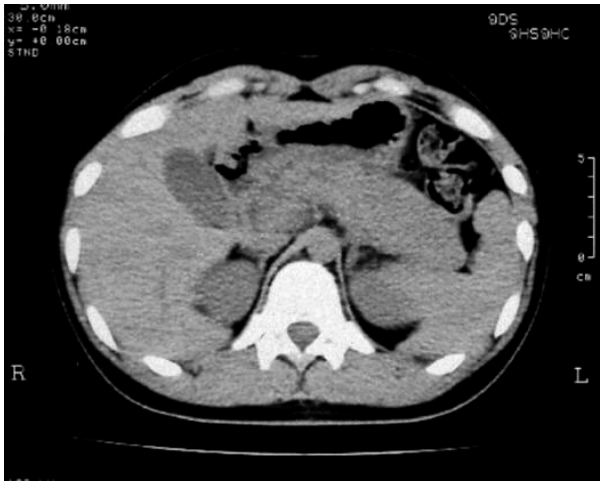

Figure 2. Computed tomography of the pancreas. The CT image shows the diffusely enlarged pancreas with its so-called "sausage-like" appearance before treatment.

fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) shows accumulative signals in the pancreatic lesions similar to the imaging of pancreatic cancer [22]. ERCP images in the AIP patients show segmental or diffuse narrowing of the main pancreatic duct (Figure 3) [9, 10, 11, 12, 13, 14]. On the other hand, the pancreas often shows atrophic changes after steroid treatment. This may be due to the improvement of pancreatic edema with acinar atrophy. Although magnetic resonance cholangio-pancreatography (MRCP) does not adequately show the narrowing or stenosis of the pancreatic duct, it can well demonstrate images of the CBD. Patients with AIP often show stenosis of the intra-pancreatic CBD

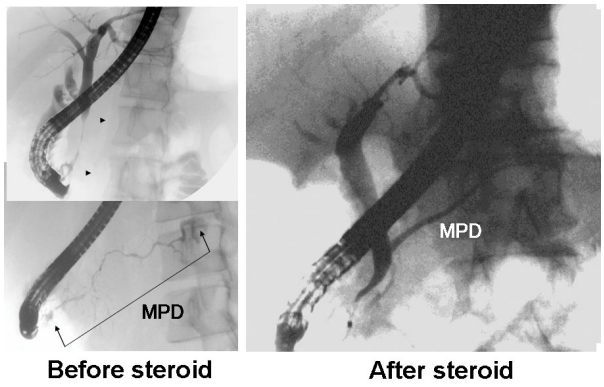

Figure 3. ERCP images of autoimmune pancreatitis and effects of steroid therapy. Both the narrowing main pancreatic duct and intra-pancreatic common bile duct improved one month after steroid therapy.

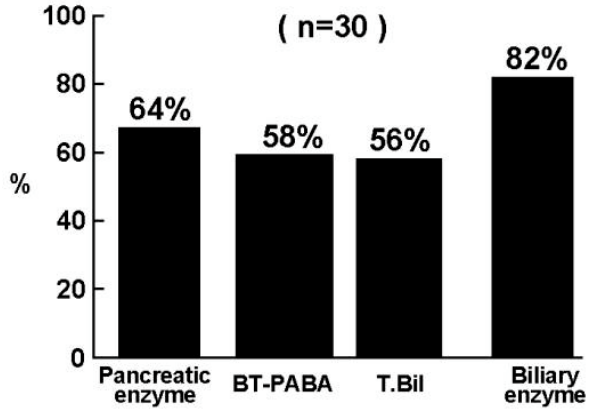

Figure 4. Laboratory data in 30 patients with autoimmune pancreatitis. The laboratory data of our 30 cases showed the increase of serum hepatic, biliary and pancreatic enzymes, and total bilirubin in 22 (73%), 25 (83%), 19 (63%) and 16 (53%) patients, respectively. Seventeen of our 30 patients showed hypofunction (58%) by N-benzoyl-L-tyrosyl-para-aminobenzoic acid (BT-PABA) exocrine test.

resulting in dilatation of the upper-stream and. the sclerosing stenosis of the extra-pancreatic CBD similar to primary sclerosing cholangitis (PSC) [14]. Steroid therapy in AIP is usually effective for the stenosis of CBD as well as the pancreatic duct [13, 14], while it is not very effective for classic PSC [23]. These findings suggest that the stenotic mechanism of CBD in AIP may be different from that in classic PSC.

Laboratory Data (Figures 4 and 5)

Patients with AIP usually show increased pancreatic enzymes, gamma-globulin, IgG especially the IgG4 subtype [24], several

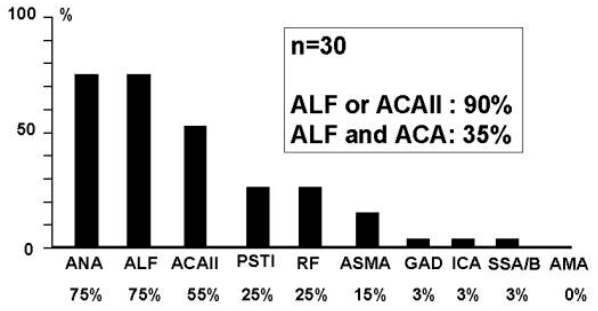

Figure 5. Autoantibodies in 30 patients with autoimmune pancreatitis. Of 30 patients, ANA was detected in 75%,, ALF in 75%, ACA-II in 55%, RF in 25% and ASMA in 15%. However, AMA was absent in all cases.

autoantibodies such as antinuclear antibody (ANA), anti-lactoferrin antibody (ALF), anti-carbonic anhydrase-II antibody (ACA-II), rheumatoid factor and anti-smooth muscle antibody [25]. Patients with jaundice or stenosis of the CBD show abnormal levels of serum bilirubin and hepatobiliary enzymes. In these cases, other liver diseases such as viral hepatitis, autoimmune hepatitis or PBC should be differentiated from AIP. The laboratory data of our 30 cases showed an increase in serum hepatic, biliary and pancreatic enzymes, and total bilirubin in 22 (73%), 25 (83%), 19 (63%) and 16 (53%) patients, respectively. The pancreatic exocrine function was slightly or moderately abnormal. Seventeen of our 30 patients showed hypofunction (58%) using an N-benzoyl-L-tyrosyl-para-aminobenzoic acid (BT-PABA) exocrine test. Most cases of diabetes mellitus were type II, not insulin dependent (NIDDM) but not type Ia, insulin dependent (IDDM) [26, 27]. After steroid therapy, many abnormal laboratory findings were reversible and many cases of DM were brought under control using steroid therapy [10, 11, 12, 13, 14, 26, 27].

Pathophysiology of AIP

Humoral Immunity and Target Antigens

The occasional coexistence of pancreatitis with other lesions suggests that there may be common target antigens in the pancreas and other exocrine organs such as the salivary gland, biliary tract and renal tubules. We identified several autoantibodies such as antinuclear antibody (ANA), anti-lactoferrin (LF) antibody (ALF), and anti-carbonic anhydrase-II (CA-II) antibody (ACA-II) by using the patient's serum and expression vector encoding human pancreatic cDNA [25]. Lactoferrin and CA-II are distributed in the various human tissues, including the lactating breast, bronchial, salivary and gastric glands, the pancreas and renal tubules [28]. We used animal models of autoimmune pancreatitis along with sialoadenitis and cholangitis using neonatally thymectomized (nTx) mice immunized with LF or CA-II and nude mice transferred with lymphocytes prepared from nTx mice [29]. The high prevalence of these auto-antibodies in animal models suggest that CA-II and LF may be the candidates for target antigens in AIP. However, it is noted that these antibodies are not necessarily specific for AIP because ACA-II can be detected in some patients with SjS or systemic lupus erythematosus [30], and ALF in ulcerative colitis or PSC [31].

Although the majority of patients with AIP show increased levels of IgG, especially the IgG4 subtype [24], the roles of IgG4 in AIP are still unclear. The majority of cases of diabetes mellitus associated with AIP show type II diabetes, while 10% of patients with diabetes mellitus show autoimmune diabetes (type Ia) due to the presence of autoantibodies against glutamic acid decarboxylase, insulin, or tyrosine phosphatase-like protein [13]. Interestingly, anti-CA-II and anti-LF are often observed in type I diabetes.

Cellular Immunity and Effector Cells

The role of the effector cells in AIP has been poorly understood. The activated CD4+ and CD8+ T-cells bearing HLA-DR and CD45RO were elevated in the peripheral blood lymphocytes (PBLs) as well as in the pancreas in AIP as compared to other causes of pancreatitis such as alcoholic or gallstone-related pancreatitis [10, 25]. CD4+ T-cells are further subdivided into Th1 and Th2 cells based on profiles of cytokine production, and these two T-cell populations counterregulate each other [32]. Thl cells, which produce IL-2, tumor necrosis factor (TNF)-a and IFN-g, mediate cellular immunity, macrophage activation, cytotoxicity and facilitate B cell production of opsonizing and complement-fixing antibodies. In contrast, Th2 cells, which produce IL-4, 5, 6 and 10, promote humoral and allergic responses [32]. Similar to SjS or PSC, CD4+ T-cells showing the Th1 type of immune response are predominantly involved in the development of AIP as effector cells over Th2 type CD4+ T-cells [24]. Similarly, Th1 immune response is

involved in the development of pancreatitis and sialoadenitis in animal models. In some patients with AIP, HLA-DR antigens are expressed on the pancreatic duct cells as well as CD4+ T-cells [10, 31, 32]. However, there is also a possibility that CD8+ T-cells may be effector cells, because HLA-DR+CD8+ T-cells as well as CD4+ T-cells increased in PBLs and infiltrated the pancreas in patients with AIP [25].

Treatment and Prognosis

In AIP patients with mild symptoms, the usual treatment for acute pancreatitis such as fasting, protease inhibitors and antibiotics is not necessarily required. In cases of jaundice, percutaneous transhepatic or endoscopic retrograde biliary drainage is often needed, especially with the complication of bacterial infection. Steroid therapy is usually effective for bile duct and salivary lesions as well as pancreatic duct lesions [9, 10, 11, 12, 13, 14, 18]. It has been noted that some patients may spontaneously improve without any treatment [14]. Some patients associated with type II diabetes mellitus may improve after steroid therapy [13]. In the cases of bile duct lesions without response to steroid therapy, surgery is often necessary in order to differentiate them from a malignancy as well as for relieving the symptoms [14]. Twenty-one of our 30 patients were treated successfully with prednisolone, two with pancreatectomy, and four without medication. The long-term prognosis of AIP is unknown. As the clinical and laboratory findings of most cases are reversible after steroid therapy [13, 14, 28], the prognosis of AIP may depend on the severity of the complications such as other autoimmune diseases or diabetes mellitus.

Conclusion

In summary, recent studies support the concept of autoimmune pancreatitis, which appears to be a unique clinical entity. Histopathologically, AIP is similar to LPSP showing fibrosis, infiltration of lymphocytes and plasmacytes, and obliterative phlebitis in the pancreas; major lymphocytes infiltrating around the pancreatic duct are T cells. Although the pathogenesis of AIP is still unknown, several hypotheses have been proposed from the clinical and animal experimental aspects. The first step in the disease may be an antigenic alteration at the pancreatic duct or acinar cells such as an aberrant expression of HLA-DR. Although the long-term prognosis of AIP is unknown, the clinical and laboratory findings of most cases are reversible after steroid therapy.

Keywords Autoimmunity; Pancreatitis; Steroids

Abbreviations ACA-II: anti-carbonic anhydrase II antibody; AIP: autoimmune-related pancreatitis; ALF: anti-lactoferrin antibody; AMA: anti-mitochondrial antibody; ANA: anti-nuclear antibody; ASMA: anti-smooth muscle antibody; BT-PABA: N-benzoyl-L-tyrosyl-para-aminobenzoic acid; CA-II: carbonic anhydrase-II; CBD: common bile duct; DM: diabetes mellitus; ELISA: enzyme-linked immunosorbent assay; ERCP: endoscopic retrograde cholangio-pancreatography; FDG: F-18 fluoro-2-deoxy-D-glucose; IDDM: insulin dependent diabetes mellitus; IFN-g: interferon-g; IL-4: interleukin-4; LF: lactoferrin; LPSP: lymphoplasmacytic sclerosing pancreatitis; mAb: monoclonal antibody; MRCP: magnetic resonance cholangio-pancreatography; NIDDM: not insulin dependent diabetes mellitus; nTx: neonatally thymectomized; PBC: primary biliary cirrhosis; PBL: peripheral blood lymphocyte; PET: positron emission tomography; PNPD: pancreatitis showing the narrowing appearance of the pancreatic duct; PSC: primary sclerosing cholangitis; RA: rheumatoid arthritis; RF: rheumatoid factor; SjS: Sjögren's syndrome

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